

REMARKS

Foremost, Applicants thank Examiners Kallis, Fox and Nelson for the courtesies extended in the interview of March 11, 2004.

Claim 26 is canceled without prejudice or disclaimer. Claims 23, 31, 33, 35, 36 and 37 are amended, as follows:

Claim 23 is amended to incorporate the recitation found in claim 26, that the maltogenic alpha-amylase has at least 70% identity to amino acids 34-719 of SEQ ID NO:2, and claim 26 has accordingly been canceled.

Claim 31 is amended to incorporate the recitation found in claim 33, subpart (b), that the maltogenic alpha-amylase has at least 70% identity to amino acids 34-719 of SEQ ID NO:2, and claim 33 is amended to delete this recitation.

Claim 35 is amended to incorporate the recitation found in claim 36, subpart (b), that the maltogenic alpha-amylase has at least 70% identity to amino acids 34-719 of SEQ ID NO:2, and claim 36 is amended to delete this recitation.

Claim 37 has been amended to depend from claim 36 instead of non-existent claim 46.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments, the following remarks and the accompanying Declaration of Dr. Joel Cherry is requested.

I. Election/Restriction

The Examiner states that the Applicants' assertion of mistaken identity as to what enzyme is disclosed in Vickers is not persuasive because Vickers teaches a plant transformed with "some type of amylase gene possessing some kind of maltogenic properties" and that "Applicant's teaching are not an advance over the prior art."

Vickers does not disclose a maltogenic alpha-amylase, rather, Vickers discloses an alpha-amylase. A maltogenic alpha-amylase is a different enzyme than the alpha-amylase of Vickers, having different enzymatic activity and different enzyme classifications. A maltogenic alpha-amylase, recited in the claims of the present invention, is the common name for the enzymes generally classified under EC 3.2.1.133. An alpha-amylase, which is cited in Vickers and in many of the other references relied upon by the Examiner, is generally classified under EC 3.2.1.1. The classifications of EC 3.2.1.1 and E.C.3.2.1.133 are attached herewith as Exhibit A and B, respectively.

Confirmation that Vickers does not teach a maltogenic alpha amylase, is evidenced by the fact that Vickers specifically references Applicants' TERMAMYL® product as a source for a *B. licheniformis* alpha-amylase. Applicants' TERMAMYL® product, as confirmed in, e.g., U.S. Patent No. 5,989,169, attached herewith as Exhibit C, is unquestionably an alpha-amylase not a maltogenic alpha amylase.

Accordingly, the assertion that Vickers discloses a maltogenic alpha-amylase is factually incorrect, and clarification of the record is respectfully requested.

II. The Rejection of Claims 23-27 under 35 U.S.C. 112 (Written Description)

Claims 23-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification. The Examiner alleges the following:

Applicants assertion that numerous maltogenic alpha-amylases are described in the specification that have at least 70% sequence identity to SEQ ID NO:2 is not supported by the teachings of the specification and are speculative in nature. Nowhere in the cited pages of the specification does Applicant provide any one to one comparison of the broadly claimed and non-exemplified genus of amino acid sequences having maltogenic activity and at least 70% sequence identity to SEQ ID NO:2.

Applicants assert that many of the variants described in the U.S. Patent 6,162,628 were in fact made. The variants described in the '628 Patent are based upon one exemplified maltogenic alpha-amylase protein sequence form a single bacterial sequence and as argued above there is no one to one comparison of the sequences of the '628 Patent or the variants of the instant specification to SEQ ID NO:2. In addition, Applicants provide no guidance as to which combination of the vast myriad of amino acid substitutions cited in the specification would recover maltogenic alpha-amylase activity.

Further, the '628 patent deals with variations over the entire range of the amino acid sequence while the instant Application only claims a range cover amino acids 34 to 719 of SEQ ID NO:2. Furthermore, the '628 patent deals with proteins while the claims of the instant Application are drawn to the genes encoding proteins. Moreover, the '628 patent does not provide conserved sequences of the genes which are correlated with function, as per MPEP 2163 and Written Description Guidelines.

The '628 patent is insufficient to support the written description or enablement of the instant claims. The instant specification and prior should provide enabling disclosure. See *Genentech, Inc. v. Novo Nordisk, A/S*, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997), which teaches that disclosure of a "mere germ of an idea does not

constitute [an] enabling disclosure”, and that “the specification, not the mere knowledge of one skilled in the art” must supply the enabling aspects of the invention.

The written description requirement of the Patent Code is fulfilled when the patent specification describes the claimed invention in sufficient detail such that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). The written description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See *In re Marzocchi*, 169 USPQ 367 (CCPA 1971).

The specification of the instant application discloses that the present invention is directed, among other things, to transgenic cereal plants, transgenic cereal plant cells and transgenic cereal plant seeds comprising a nucleic acid sequenced encoding a maltogenic alpha-amylases, including a maltogenic alpha-amylase having at least 70% identity to SEQ ID NO:2. See the specification at page 4, line 20 to page 5, line 10. The specification discloses both the nucleic acid sequence and the amino acid sequence for a maltogenic alpha-amylase from *B. stearothermophilus*, as SEQ ID NO:1 and SEQ ID NO:2, respectively. The specification also references the biological deposit for this gene, namely, that the coding sequence for this maltogenic alpha-amylase may be obtained from strain DSM 11837.

The specification also describes at page 7 to page 19 many variants of SEQ ID NO:2, which are also applicable to other homologous maltogenic alpha-amylases (e.g., sequences which have at least 70% identity to amino acids 34-719 of SEQ ID NO:2), including both single alterations and combinations of alterations. In this regard, the maltogenic alpha amylase variants described are evidence of the possession of maltogenic alpha-amylase sequences required to practice the claimed invention.

The specification also references, at page 6, WO 99/43794 (corresponding to US Patent No. 6,162,628) which also discloses numerous maltogenic alpha-amylase variants, made by colleagues in Applicants' company. The '628 patent has a detailed listing of many variants as well as the nucleic acid sequence and the amino acid sequence for a maltogenic alpha-amylase from *B. stearothermophilus*. The '628 patent also describes how one skilled in the art can make the maltogenic alpha amylase variants, including obtaining the DNA encoding same. See the '628 patent at col. 17 to 25. Thus, the specification of the instant case and the referenced U.S. Patent

No. 6,162,628 together disclose hundreds of different maltogenic alpha amylases, including how to obtain nucleic acid sequences encoding these maltogenic alpha-amylases.

As discussed during the interview, the Examiner acknowledges that both the '628 patent and the present specification disclose many maltogenic alpha amylase proteins, however, the Examiner states that the claims are directed to nucleic acids, in particular, transgenic cereal plants, cells and seeds comprising nucleic acid sequences encoding maltogenic alpha amylases, and the Examiner requests clarification as to where the specification establishes that the inventors were in possession of nucleic acids encoding functional maltogenic alpha-amylase variants other than the nucleic acid of SEQ ID NO:1.

As Applicants have provided the nucleic acid sequence of SEQ ID NO:1, and have identified many maltogenic alpha-amylases variants of this sequence, it would simply be routine in the art for the Applicant to obtain nucleic acid sequences encoding these maltogenic alpha-amylase, for example, by using SEQ ID NO:1 to prepare nucleic acids encoding the maltogenic alpha-amylase variants. In this regard, Applicants respectfully submit the Declaration of Dr. Joel Robert Cherry, one of the co-inventors of the '628 patent. As provided in Dr. Cherry's declaration, the disclosure of the amino acid sequences of the maltogenic alpha-amylase variants is clearly sufficient to place the artisan in possession of the nucleic acids encoding these sequences given that the nucleic acid sequence of SEQ ID NO:1 is provided. As Dr. Cherry further discloses such preparation of these nucleic acid sequences is routine for the skilled artisan. In this regard, it is a well established that you do not have to disclose that which is well known to one skilled in the art. See *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1332 (Fed. Cir. 2003) and Interim Guidelines for the Examination of Patent Applications Under The 35 U.S.C. 112, ¶ 1 'Written Description' Requirement.

With respect to the Examiner's request for confirmation that the specification discloses nucleic acid sequences encoding functional maltogenic alpha-amylases, in his declaration, Dr. Cherry confirms that the specification of the instant application and the '628 patent describe functional maltogenic alpha-amylases. Dr. Cherry also confirms, as requested by the Examiner, that variants described in the examples of the '628 were functional maltogenic alpha amylases, which can be confirmed by carrying out the assay described in the '628 patent at col. 23, line 60, to col. 25, line 15.

Accordingly, the specification clearly provides a written description evidencing that Applicants were in possession of nucleic acid sequences encoding functional maltogenic alpha-

amylase variants, including nucleic acid sequences encoding maltogenic alpha amylase that have at least 70% identity to amino acids 34-719 of SEQ ID NO:2.

With respect to the production of transgenic cereal plants, plant cells and seeds encoding the nucleic acids encoding the maltogenic alpha-amylases, the specification discloses at page 14-20 and in the Examples how to prepare transgenic cereal plants, plant cells and seeds comprising these nucleic acids.

Therefore, the specification provides a written description which shows that the Applicants were in possession of both (1) numerous nucleic acid sequences encoding functional maltogenic alpha amylase and (2) methods for preparing transgenic cereal plants, cells and seeds comprising such sequences, such that one skilled in the art can reasonably conclude that the inventors had possession of the claimed invention.

Notwithstanding that Applicants' specification clearly provides sufficient written description support to show that Applicants were in possession of the claimed invention, Applicants also rebut each of the specific grounds relied upon by the Examiner for the rejection in the Office Action, as follows:

The Examiner contends: *"Applicants assertion that numerous maltogenic alpha-amylase are described in the specification that have at least 70% sequence identity to SEQ ID NO:2 is not supported by the teachings of the specification and are speculative in nature."*

This is not correct. As discussed above, Applicants specification clearly describes that Applicants were in possession of nucleic acids encoding maltogenic alpha-amylase that have at least 70% sequence identity to SEQ ID NO:2.

The Examiner contends: *"Nowhere in the cited pages of the specification does Applicant provide any one to one comparison of the broadly claimed and non-exemplified genus of amino acid sequences having maltogenic activity and at least 70% sequence identity to SEQ ID NO:2."*

Contrary to this statement, as discussed above, the genus is exemplified, including disclosing hundreds of different maltogenic alpha-amylases. This description clearly establishes that Applicants were in possession of a vast number of species of maltogenic alpha-amylases. It is also not seen why a "one-to-one" comparison is necessary to satisfy the written description requirement. Applicants are not required to disclose every embodiment, but merely to provide a written description sufficient to show that Applicants had possession of the claimed invention.

The Examiner contends: *"Applicants assert that many of the variants described in the U.S. Patent 6,162,628 were in fact made. The variants described in the '628 Patent are based upon one exemplified maltogenic alpha-amylase protein sequence form a single bacterial sequence*

and as argued above there is no one to one comparison of the sequences of the '628 Patent or the variants of the instant specification to SEQ ID NO:2."

The variants in the '628 Patent were based upon one specific maltogenic alpha-amylase protein, however, as explained by Dr. Cherry, the genus of maltogenic alpha-amylase protein is a very small genus. That is, there are only a limited number of wild-type maltogenic alpha-amylase proteins known, and in this regard, a representative number has clearly been provided.

Furthermore, it is also not clear what relevance a "one-to-one" comparison has to the issue of written description, as Applicants are not required to disclose every embodiment, but merely to provide a written description sufficient to show that Applicants had possession of the claimed invention.

The Examiner contends: *"In addition, Applicants provide no guidance as to which combination of the vast myriad of amino acid substitutions cited in the specification would recover maltogenic alpha-amylase activity."*

The specification and the cited patent application disclose both many single alterations and combinations of alterations that result in a maltogenic alpha-amylase. However, it is not clear and the Examiner has not explained why an artisan needs to determine all the possible combinations of the single alterations (that is, in addition to the ones exemplified) that work well together in order to practice the claimed invention.

The Examiner contends: *"The '628 patent deals with variations over the entire range of the amino acid sequence while the instant Application only claims a range cover amino acids 34 to 719 of SEQ ID NO:2."*

Amino acids 34 to 719 do equate exactly with amino acids 1-686 of SEQ ID NO:1 of the '628 patent. The sequence listing of the Patent Office's sequence listing program generated the wrong mature peptide, even though the mature peptide was defined by the coding sequence nucleotide 100 to nucleotide 2157.

The Examiner contends: *"Moreover, the '628 patent does not provide conserved sequences of the genes which are correlated with function, as per MPEP 2163 and Written Description Guidelines."*

This statement is clearly not correct. The '628 patent discloses numerous important conserved sequences of the genes which are important for function, including:

-identifying the domains, and which amino acids make up the domains (see col. 4, lines 40-48);

-identifying the domain (domain A) which contains the active residues, and identifying the three-dimensional structure for this domain, and even the residues which make up the active site (see col. 4, lines 50-67),

-identifying the number and location of the calcium ions (see col. 5, lines 33-35),

-identifying the residues which are involved in substrate binding (see col. 5, lines 56 to col. 6, line 15),

-identifying which alterations can be made to improve various properties of a maltogenic alpha amylase of SEQ ID NO:2 and homologous structures, such as, pH dependency, stability, temperature dependent activity, cleavage pattern, improved starch retrogradation and anti-staling properties (see, *inter alia*, col. 6 to col. 15).

Furthermore, WO 99/15636 discloses the nucleic acid sequences and amino acid sequences (E domain and D domain), which correspond to the binding domain for maltogenic alpha-amylases.

The Examiner cites MPEP 2163 and the Written Description Guidelines as supporting that the claims lack adequate written description. However, the Examiner is respectfully directed to MPEP 2163, which clearly states:

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice,..., or by disclosure of relevant identifying characteristics, i.e., structures or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the application was in possession of the claimed genus. [Citing *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.]

In this regard, MPEP 2163 describes exactly what applicants have provided in their specification, namely:

-providing a representative number of species of the genus of a maltogenic alpha-amylase including maltogenic alpha-amylases having at least 70% identity to SEQ ID NO:1, (see the over 100 different maltogenic alpha-amylase disclosed), and, as discussed above, the artisan would readily be able to obtain nucleic acid sequences encoding same;

-providing relevant identifying characteristics, such as, structure and other physical properties (see the detailed description of the nucleic acid sequence, protein sequence, the three dimensional structure of a particular maltogenic alpha-amylase and the identity of the domains which make up the structure);

-providing functional characteristics coupled with known structure (see the correlation of the domains and particular amino acids with a function).

The Examiner contends: *"The '628 patent is insufficient to support the written description or enablement of the instant claims. The instant specification and prior should provide enabling disclosure. See Genentech, Inc. v Novo Nordisk, A/S, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997), which teaches that disclosure of a "mere germ of an idea does not constitute [an] enabling disclosure", and that "the specification, not the mere knowledge of one skilled in the art" must supply the enabling aspects of the invention."*

Foremost, it is not merely the '628 patent but also the present specification of the instant application that provides the written description support, as previously discussed. Furthermore, the cited case addresses enablement, whereas the rejection at issue is a written description rejection. Enablement and written description are two different standards, and the Examiner has not explained how the cited case law on enablement specifically has relevance to the separate legal requirement of written description.

Accordingly, Applicants respectfully submit that the specification provides a written description which shows that Applicants were in possession of numerous nucleic acid sequences encoding maltogenic alpha amylases and methods for preparing transgenic cereal plants, transgenic cereal plant cells, and transgenic seeds comprising these sequences, such that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

III. The Rejection of Claims 23-37 under 35 U.S.C. 112 (Enablement)

Claims 23-37 are rejected under 35 U.S.C. 112, as allegedly lacking enablement. The Examiner alleges:

Applicant asserts that the claims are directed to transgenic cereal cells not sequences and since the broadly claimed variants can be made without undue experimentation the transgenic cells and plants of the invention are enabled (response pages 7-8). Since Applicant has not described the claimed sequences of the invention as argued supra, Applicant has not taught how to make the broadly claimed sequences of the invention and the host cells and plants therewith.

Applicant's assertion that the Sweetlove experiments involving over expression of ADP glucose pyrophosphorylase have no

bearing on Applicant's ability to make transgenic plants is acknowledged....However, Applicants has also claimed an amount of maltogenic alpha-amylase effective to delay staling of baked bread, requiring that the claimed variants have maltogenic activity in a plant, and not just their mere presence. This argument is supported by Applicant's assertion that the amount of enzyme may have relevance to the application of the transgenic plants.

Applicant further asserts that the amount of experimentation to practice the invention is routinely encountered in the art, and since the nature of experimentation is only finding suitable materials such as promoters and host cells, the claims are thus enabled. The claims are broadly drawn to sequences comprising any number of substitutions covering as much as 30% of the amino acid sequence of SEQ ID NO:2. Given the lack of teaching of which amino acid substitutions comprising a variant having 70% sequence identity to SEQ ID NO:2 without any teaching as to which combination of substitutions could be predictably eliminate, one of skill in the art would be required to test a myriad of variants for maltogenic activity of the broadly claimed genus having 70% sequence identity, and thus the claims are not enabled.

This rejection is respectfully traversed. To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. See *Genentech, Inc. v Novo Nordisk, A/S*, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997). Noteworthy, the test for determining enablement is not whether *any* experimentation is required, but rather whether *undue* experimentation is required. Indeed, as noted by the *In re Wands* court (*In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), the test for determining whether undue experimentation is required even permits a considerable amount of testing.

As previously discussed, the specification discloses numerous representative examples of maltogenic alpha-amylases and provides a detailed teaching including at page 14-20 and in the Examples of how to take genes encoding maltogenic alpha amylase and to prepare transgenic cereal plants and transgenic cereal plant cells comprising these genes. Clearly, a skilled artisan is able to practice the claimed invention commensurate in scope with the claims as Applicants provide the artisan numerous species of maltogenic alpha-amylases, including, both protein and nucleic acids sequences, which are representative of the scope of the claims. The specification also teaches how to prepare transgenic cereal plants, cereal plants cells and seeds comprising these genes.

Applicants are not required to describe each and every embodiment of the invention, but rather only teach the artisan how to practice the invention, providing a representative number of embodiments. There is no evidence in record that an artisan would be unable to produce a transgenic cereal plants, cells and/or seeds comprising nucleic acids encoding the numerous maltogenic alpha-amylases disclosed in the specification.

However, notwithstanding that Applicants' specification provides enablement that is commensurate in scope with the claims, Applicants also rebut the specific grounds relied upon by the Examiner for the rejection in the Office Action, as follows:

The Examiner contends: *"Since Applicant has not described the claimed sequences of the invention as argued supra, Applicant has not taught how to make the broadly claimed sequences of the invention and the host cells and plants therewith."*

Applicants, however, are not required to describe each and every embodiment, but rather must only teach the artisan how to practice the invention, and provide a representative number of embodiments. Applicants have clearly provided a representative number of species of maltogenic alpha amylases to show that they were in possession of many nucleic acid sequences encoding maltogenic alpha-amylases suitable for use in preparing transgenic cereal plants, cells and seeds encoding same. Moreover, there is no evidence in record that an artisan would be unable to produce a transgenic cereal plants, cells or seeds comprising any of the numerous maltogenic alpha-amylases disclosed in the specification or to maltogenic alpha-amylase in general.

The Examiner contends: *"Applicant's assertion that the Sweetlove experiments involving overexpressoin of ADP glucose pyrophosphoreylase have no bearing on Applicant's ability to make transgenic plants is acknowledged....However, Applicants has also claimed an amount of maltogenic alpha-amylase effective to delay staling of baked bread, requiring that the claimed variants have maltogenic activity in a plant, and not just their mere presence. This argument is supported by Applicant's assertion that the amount of enzyme may have relevance to the application of the transgenic plants."*

The Examiner's statement is, at best, only relevant to claims 34 and 35 as these are the only claims that recite an amount effective to delay staling. Nevertheless, as specifically disclosed in the specification, the surprising benefit of a "maltogenic alpha-amylase" over an "alpha-amylase" is that it can be dosed broadly. The maltogenic alpha-amylase is particularly suitable for transgenic expression in plants in that high dosages of this enzyme are not a problem. See the specification at page 3 line 21 to page 4, line 20."

The Examiner contends: *"Applicant further asserts that the amount of experimentation to practice the invention is routinely encountered in the art, and since the nature of experimentation is only finding suitable materials such as promoters and host cells, the claims are thus enabled. The claims are broadly drawn to sequences comprising any number of substitutions covering as much as 30% of the amino acid sequence of SEQ ID NO:2. Given the lack of teaching of which amino acid substitutions comprising a variant having 70% sequence identity to SEQ ID NO:2 without any teaching as to which combination of substitutions could be predictably eliminated, one of skill in the art would be required to test a myriad of variants for maltogenic activity of the broadly claimed genus having 70% sequence identity, and thus the claims are not enabled."*

The test for determining enablement is not whether *any* experimentation is required, but rather whether *undue* experimentation is required, and as, stated by the *In re Wands* court (*In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), the test for determining whether undue experimentation is required even permits a considerable amount of testing. The artisan wanting to practice the claimed invention simply needs to follow the teachings of the instant specification to obtain nucleic acids encoding maltogenic alpha-amylase of a scope referenced in the claims and to introduce these sequences into cereal plants, cells and seeds. In this regard, and given this detailed guidance, it is clear that only routine experimentation would be required to practice the claimed invention to obtain a transgenic cereal plant, cell or seed comprising a nucleic acid sequence encoding a maltogenic alpha amylase.

IV. The Rejection of Claims 23-37 under 35 U.S.C. 103

Claims 23-37 are rejected under 35 U.S.C. 103 as obvious over Pen J. WO 91/14772, in view of Barrow F, Nature Biotechnology, and further in view of Accession number p19532, Diderichsen and Christophersen et al.

The Examiner contends that the motivation to include a maltogenic alpha-amylase gene in a transgenic cereal plant comes from the knowledge that maltogenic alpha-amylase genes are known to be useful for baking. The rejection is clearly based on hindsight. Simply because it is known that a gene encodes a protein that has beneficial properties in baking does not lead to a conclusion that it is suitable for use in making a transgenic cereal plants, cells or seeds.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 103. Applicants respectfully request reconsideration and withdrawal of the rejection.

V. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

Date: May 3, 2004



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Attorney Docket No.: 5753.204-US

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Nielsen et al.

Confirmation No: 7015

Serial No.: 09/831,656

Group Art Unit: 1638

Filed: May 11, 2001

Examiner: Kallis, Russell

For: Transgenic Plant Expressing Maltogenic Alpha-Amylase

DECLARATION OF DR. JOEL CHERRY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Joel Cherry, do hereby state and declare that:

1. I am a citizen of the United States residing at 3319 Morro Bay Avenue, Davis, California. I am currently employed with Novozymes Biotech, Inc. of Davis, California in the position of Director, Biotechnology and Bioenergy.

2. I have a degree in chemistry from Carleton College and a PhD in biochemistry from the University of New Hampshire. I have expertise in the field of nucleic acid and protein engineering of enzymes, and extensive experience in engineering maltogenic alpha amylases. I am the author or co-author of many publications, including: Cherry, JR, Hondred, D, Keller, J, Hershey, HP, & Vierstra, RD (1990) "Use of transgenic plants to study phytochrome domains involved in structure and function" in *Phytochrome Properties and Biological Action* (NATO-ASI series Series H, Cell Biology, vol. 50) B Thomas & CB Johnson, Eds., Springer-Verlag, Berlin, pp. 113-127.

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I am also an inventor on many patent applications, including U.S. Patent No. 6,162,628, entitled "Maltogenic Alpha-Amylase Variants" and U.S. Patent No. 6,482,622, entitled "Amylolytic Enzyme Variants."

3 Although I am not an inventor of the above-captioned application, directed to transgenic plants, cells and seeds encoding maltogenic alpha amylases, I am, nevertheless familiar with the inventions described and claimed in this patent application.

4 U.S. Patent No. 6,162,628, which is referenced in the above captioned application on page 6 (by the corresponding international application no. WO 99/43794), discloses and claims numerous maltogenic alpha amylases. The genus of maltogenic alpha-amylase is a very small genus, that is, there are relatively few wild type maltogenic alpha amylase genes known in the art as compared, for example, to the genus of the alpha-amylases, proteases, or cellulases. We generally focused our work on *Bacillus stearothermophilus* maltogenic alpha-amylase, which is representative of the known maltogenic alpha-amylases.

5 The work underlying the subject matter described in U.S. Patent No. 6,162,628 entailed, among other things, determining suitable amino acid alterations and accordingly nucleic acid alterations which can be made to improve the properties of maltogenic alpha-amylases. Our work involved both structural analysis, e.g., analyzing the sequence and three dimensional structure of maltogenic alpha amylases, and functional analysis, that is, producing and testing the maltogenic alpha amylases we discovered by producing nucleic acids encoding the maltogenic alpha-amylases, expressing these genes, and testing the maltogenic alpha amylases in various functional assays. Our work was very successful, resulting in the discovery of numerous new maltogenic alpha amylases, and identifying many alterations which can improve the *Bacillus stearothermophilus* maltogenic alpha-amylase and homologous sequences thereof.

6. As a result of our work, we produced thousands of new maltogenic alpha-amylase variants with activity on starch. Although we did not test all of these variants for production of maltose, we tested a sample, which were determined to be maltogenic. It is my opinion that the vast majority of the variants we produced retained maltogenic alpha-amylase activity, as can be determined by carrying out the assay described in U.S. Patent No. 6,162,628 at col. 23, line 60, to col. 25, line 15. Examples of some of the functional maltogenic alpha-

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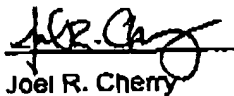
T-387 P.05/06 F-451


amylases that we produced are described in col. 11 to col. 14 and in Examples 1-7. In addition to having maltogenic alpha-amylase activity, many of these new maltogenic alpha amylases also had improved properties as compared to the *Bacillus stearothermophilus* maltogenic alpha-amylase, which are also described in U.S. Patent No. 6,162,628.

7. U.S. Patent No. 6,162,628 and the specification of the above-captioned application (which references our work in U.S. Patent No. 6,162,628) generally describe the maltogenic alpha-amylases on the basis of their amino acid sequences rather than their nucleic acid sequences. Nevertheless, the disclosure of the nucleic acid sequence of the maltogenic alpha-amylase of SEQ ID NO:1 and the protein sequences of the variants of this sequence are clearly sufficient to place the skilled artisan in possession of the nucleic acids encoding these sequences. An artisan, for example, would be able to produce these nucleic acid sequences by using the nucleic acid sequence of SEQ ID NO:1 (DSM 11837) and introducing nucleic acid changes which encode for the desired amino acid changes, as described in our patent. The skills required to prepare nucleic acid sequences encoding the maltogenic alpha-amylase proteins based on the information provided in the specification of U.S. Patent No. 6,162,628 and the specification of the above-captioned application are routine for the skilled practitioner. In this regard, it is clear that the skilled artisan would conclude that the Applicants of the above-captioned application were also in possession of these nucleic acids encoding the maltogenic alpha amylase proteins described in the specification of the above captioned application and in U.S. Patent No. 6,162,628.

8. The undersigned declarant declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize any patent issuing thereon.

Signed this 30th day
of April, 2004


Joel R. Cherry

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ENZYME: EC 3.2.1.1


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ID 3.2.1.1
 DE Alpha-amylase.
 AN 1,4-alpha-D-glucan glucanohydrolase.
 AN Glycogenase.
 CA Endohydrolysis of 1,4-alpha-glucosidic linkages in oligosaccharides
 CA and polysaccharides.
 CC -!- Acts on starch, glycogen and related polysaccharides and
 CC oligosaccharides in a random manner; reducing groups are liberated
 CC in the alpha-configuration.
 DR BRENDA; [3.2.1.1](#).
 DR EMP/PUMA; [3.2.1.1](#).
 DR WIT; [3.2.1.1](#).
 DR KYOTO UNIVERSITY LIGAND CHEMICAL DATABASE; [3.2.1.1](#).
 DR IUBMB Enzyme Nomenclature; [3.2.1.1](#).
 DR [P27935](#), AM2A_ORYSA; [P27932](#), AM3A_ORYSA; [P27937](#), AM3B_ORYSA;
 DR [P27939](#), AM3C_ORYSA; [P27933](#), AM3D_ORYSA; [P27934](#), AM3E_ORYSA;
 DR [P27940](#), AMC1_ORYSA; [P27941](#), AMC2_ORYSA; [P53354](#), AMY1_AEDAE;
 DR [P22630](#), AMY1_AERHY; [P19269](#), AMY1_DEBOC; [P09961](#), AMY1_DICTH;
 DR [P25718](#), AMY1_ECOLI; [P00693](#), AMY1_HORVU; [Q01117](#), AMY1_LIPKO;
 DR [P17654](#), AMY1_ORYSA; [P21567](#), AMY1_SACFI; [Q09840](#), AMY1_SCHPO;
 DR [Q08806](#), AMY2_DEBOC; [P14898](#), AMY2_DICTH; [P26612](#), AMY2_ECOLI;
 DR [P04063](#), AMY2_HORVU; [P26613](#), AMY2_SALTY; [O42918](#), AMY2_SCHPO;
 DR [P14899](#), AMY3_DICTH; [P04747](#), AMY3_HORVU; [O14154](#), AMY3_SCHPO;
 DR [P08117](#), AMY3_WHEAT; [P04748](#), AMY4_HORVU; [Q9Y7S9](#), AMY4_SCHPO;
 DR [P04749](#), AMY5_HORVU; [P04750](#), AMY6_HORVU; [P41131](#), AMYA_AERHY;
 DR [Q02905](#), AMYA_ASPAW; [P56271](#), AMYA_ASPNG; [P10529](#), AMYA_ASPOR;
 DR [P54215](#), AMYA_DROMA; [P08144](#), AMYA_DROME; [P51548](#), AMYA_DROYA;
 DR [Q59006](#), AMYA_METJA; [Q9V298](#), AMYA_PYRAB; [P49067](#), AMYA_PYRFU;
 DR [O57932](#), AMYA_PYRHO; [P17859](#), AMYA_VIGMU; [Q02906](#), AMYB_ASPAW;
 DR [P81641](#), AMYB_DROME; [P21543](#), AMYB_PAEPO; [P19961](#), AMYC_HUMAN;
 DR [P04746](#), AMYP_HUMAN; [P00688](#), AMYP_MOUSE; [P00690](#), AMYP_PIG ;
 DR [P00689](#), AMYP_RAT ; [P83053](#), AMYP_STRCA; [O18344](#), AMYR_DROAN;
 DR [O77011](#), AMYR_DROAP; [O77020](#), AMYR_DROAV; [O77019](#), AMYR_DROBA;
 DR [O76284](#), AMYR_DROBC; [Q9NJN8](#), AMYR_DROBP; [O77021](#), AMYR_DRODO;
 DR [O77012](#), AMYR_DROEC; [Q9NJP0](#), AMYR_DROEL; [O76265](#), AMYR_DROER;
 DR [Q9GQV3](#), AMYR_DROJA; [O77013](#), AMYR_DROKI; [O76262](#), AMYR_DROLN;
 DR [O77014](#), AMYR_DROMA; [O18408](#), AMYR_DROME; [O77015](#), AMYR_DROOR;
 DR [O77022](#), AMYR_DROPN; [O18552](#), AMYR_DROPS; [O76261](#), AMYR_DROSE;
 DR [O77016](#), AMYR_DROSI; [O76459](#), AMYR_DROSR; [O18420](#), AMYR_DROSU;
 DR [O76260](#), AMYR_DROTE; [O77018](#), AMYR_DROTK; [Q9NJN7](#), AMYR_DROVA;
 DR [O76263](#), AMYR_DROWI; [O76264](#), AMYR_DROYA; [P04745](#), AMYS_HUMAN;
 DR [P00687](#), AMYS_MOUSE; [P29957](#), AMY_ALTHA ; [P30292](#), AMY_ASPSH ;
 DR [P00692](#), AMY_BACAM ; [P08137](#), AMY_BACCI ; [P06278](#), AMY_BACLI ;
 DR [P20845](#), AMY_BACME ; [P06279](#), AMY_BACST ; [P00691](#), AMY_BACSU ;
 DR [P30269](#), AMY_BUTFI ; [P23671](#), AMY_CLOAB ; [P49274](#), AMY_DERPT ;
 DR [P91778](#), AMY_PECMA ; [P30270](#), AMY_STRGR ; [P08486](#), AMY_STRHY ;
 DR [Q05884](#), AMY_STRLI ; [P09794](#), AMY_STRLM ; [P27350](#), AMY_STRTL ;

DR [P22998](#), AMY_STRVL ; [P56634](#), AMY_TENMO ; [P29750](#), AMY_THECU ;
 DR [P09107](#), AMY_TRICA ; [P38939](#), APU_THEET ; [P36905](#), APU_THESA ;
 DR [P38536](#), APU_THETU ; [P16950](#), APU_THETY ;
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NiceZyme View of ENZYME: EC 3.2.1.1


| | |
|---|---|
| Official Name | |
| Alpha-amylase. | |
| Alternative Name(s) | |
| 1,4-alpha-D-glucan glucanohydrolase. Glycogenase. | |
| Reaction catalysed | |
| Endohydrolysis of 1,4-alpha-glucosidic linkages in oligosaccharides and polysaccharides. | |
| Comments | |
| * Acts on starch, glycogen and related polysaccharides and oligosaccharides in a random manner; reducing groups are liberated in the alpha-configuration. | |
| Cross-references | |
| Biochemical Pathways; map number(s) | A6 |
| BRENDA | 3.2.1.1 |
| EMP/PUMA | 3.2.1.1 |
| WIT | 3.2.1.1 |
| KYOTO UNIVERSITY LIGAND CHEMICAL DATABASE | 3.2.1.1 |
| IUBMB Enzyme Nomenclature | 3.2.1.1 |
| MEDLINE | Find literature relating to 3.2.1.1 |
| | <p> P27935, AM2A_ORYSA; P27932, AM3A_ORYSA; P27937, AM3B_ORYSA; P27939, AM3C_ORYSA; P27933, AM3D_ORYSA; P27934, AM3E_ORYSA; P27940, AMC1_ORYSA; P27941, AMC2_ORYSA; P53354, AMY1_AEDAE; P22630, AMY1_AERHY; P19269, AMY1_DEBOC; P09961, AMY1_DICTH; P25718, AMY1_ECOLI; P00693, AMY1_HORVU; P17654, AMY1_ORYSA; P21567, AMY1_SACFI; Q09840, AMY1_SCHPO; P14898, AMY2_DICTH; P26612, AMY2_ECOLI; P04063, AMY2_HORVU; P26613, AMY2_SALTY; O42918, AMY2_SCHPO; P14899, AMY3_DICTH; P04747, AMY3_HORVU; O14154, AMY3_SCHPO; P08117, AMY3_WHEAT; P04748, AMY4_HORVU; Q9Y7S9, AMY4_SCHPO; P04749, AMY5_HORVU; P04750, AMY6_HORVU; P41131, AMYA_AERHY; Q02905, AMYA_ASPAW; P56271, AMYA_ASPNG; P10529, AMYA_ASPOR; P54215, AMYA_DROMA; P08144, AMYA_DROME; P51548, AMYA_DROYA; Q59006, AMYA_METJA; Q9V298, AMYA_PYRAB; P49067, AMYA_PYRFU; O57932, AMYA_PYRHO; P17859, AMYA_VIGMU; Q02906, AMYB_ASPAW; P81641, AMYB_DROME; P21543, AMYB_PAEPO; P19961, AMYC_HUMAN; P04746, AMYP_HUMAN; P00688, AMYP_MOUSE; </p> |

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| Swiss-Prot | P00690, AMYP_PIG ; | P00689, AMYP_RAT ; | P83053, AMYP_STRCA; |
| | P17692, AMYR_BACS8; | O18344, AMYR_DROAN; | O77011, AMYR_DROAP; |
| | O77020, AMYR_DROAV; | O77019, AMYR_DROBA; | O76284, AMYR_DROBC; |
| | Q9NJN8, AMYR_DROBP; | O77021, AMYR_DRODO; | O77012, AMYR_DROEC; |
| | Q9NJP0, AMYR_DROEL; | O76265, AMYR_DROER; | Q9GQV3, AMYR_DROJA; |
| | O77013, AMYR_DROKI; | O76262, AMYR_DROLN; | O77014, AMYR_DROMA; |
| | O18408, AMYR_DROME; | O77015, AMYR_DROOR; | O77022, AMYR_DROPN; |
| | O18552, AMYR_DROPS; | O76261, AMYR_DROSE; | O77016, AMYR_DROSI; |
| | O76459, AMYR_DROSR; | O18420, AMYR_DROSU; | O76260, AMYR_DROTE; |
| | O77018, AMYR_DROTK; | Q9NJN7, AMYR_DROVA; | O76263, AMYR_DROWI; |
| | O76264, AMYR_DROYA; | P04745, AMYS_HUMAN; | P00687, AMYS_MOUSE; |
| | P29957, AMY_ALTHA ; | P30292, AMY_ASPSH ; | P00692, AMY_BACAM ; |
| | P08137, AMY_BACCI ; | P06278, AMY_BACLI ; | P20845, AMY_BACME ; |
| | P06279, AMY_BACST ; | P00691, AMY_BACSU ; | P30269, AMY_BUTFI ; |
| | P23671, AMY_CLOAB ; | P49274, AMY_DERPT ; | P91778, AMY_PECMA ; |
| | P30270, AMY_STRGR ; | P08486, AMY_STRHY ; | Q05884, AMY_STRLI ; |
| | P09794, AMY_STRLM ; | P27350, AMY_STRTL ; | P22998, AMY_STRVL ; |
| | P56634, AMY_TENMO ; | P29750, AMY_THECU ; | P09107, AMY_TRICA ; |
| | P38939, APU_THEET ; | P36905, APU_THESA ; | P38536, APU_THETU ; |
| | P16950, APU_THETY ; | | |

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ENZYME: EC 3.2.1.133


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ID 3.2.1.133
 DE Glucan 1,4-alpha-maltohydrolase.
 AN Maltogenic alpha-amylase.
 CA Hydrolysis of (1->4)-alpha-D-glucosidic linkages in polysaccharides so
 CA as to remove successive alpha-maltose residues from the non-reducing ends
 CA of the chains.
 CC -!- Acts on starch and related polysaccharides and oligosaccharides.
 CC -!- The product is alpha-maltose; cf. EC [3.2.1.2](#).
 DR BRENDA; [3.2.1.133](#).
 DR EMP/PUMA; [3.2.1.133](#).
 DR WIT; [3.2.1.133](#).
 DR KYOTO UNIVERSITY LIGAND CHEMICAL DATABASE; [3.2.1.133](#).
 DR IUBMB Enzyme Nomenclature; [3.2.1.133](#).
 DR [P32818](#), AMYM_BACAD; [Q04977](#), AMYM_BACLI; [P19531](#), AMYM_BACST;
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NiceZyme View of ENZYME: EC 3.2.1.133

| | |
|---|---|
| Official Name | |
| Glucan 1,4-alpha-maltohydrolase. | |
| Alternative Name(s) | |
| Maltogenic alpha-amylase. | |
| Reaction catalysed | |
| Hydrolysis of (1->4)-alpha-D-glucosidic linkages in polysaccharides so as to remove successive alpha-maltose residues from the non-reducing ends of the chains. | |
| Comments | |
| <ul style="list-style-type: none"> Acts on starch and related polysaccharides and oligosaccharides. The product is alpha-maltose; cf. EC 3.2.1.2. | |
| Cross-references | |
| BRENDA | 3.2.1.133 |
| EMP/PUMA | 3.2.1.133 |
| WIT | 3.2.1.133 |
| Kyoto University LIGAND chemical database | 3.2.1.133 |
| IUBMB Enzyme Nomenclature | 3.2.1.133 |
| IntEnz | 3.2.1.133 |
| MEDLINE | Find literature relating to 3.2.1.133 |
| Swiss-Prot | P32818 , AMYM_BACAD ; Q04977 , AMYM_BACLI ; P19531 , AMYM_BACST ; |

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